yeasts have rewired many regulatory networks, such that processes as diverse as ribosomal protein gene regulation, galactose metabolism and mating-type switching, which appear to be very similar at the physiological level, are regulated by different transcription factors that bind to different regulatory sequences.

Despite its evolutionary distance to *S. cerevisiae* being *relatively* short, *C albicans*, like other members of the 'CUG' clade, has a genetic code with a non-standard codon — CUG encodes serine rather than the conventional leucine — obviating the direct use of many genetic markers from heterologous organisms such as *S. cerevisiae*. This obstacle has been overcome by the development of codon-optimized markers, fluorescent proteins and other epitope tags, which can be inserted into the genome by several approaches all ultimately involving homology-based recombination. These tools have led to many of the important advances in our understanding of the molecular mechanisms specifying mating, white-opaque switching, biofilm formation and other processes important for pathogenicity and virulence. There are clearly many more to come.

Where can I find out more?

Berman, J., and Hadany, L. (2012). Does stress induce (para)sex? Implications for *Candida albicans* evolution. Trends Genet. http://dx.doi.org/10.1016/j.tig.2012.01.004.

Broad Fungal Genome Initiative: http://www.broad.mit.edu/node/304

CandidaDB: http://genodb.pasteur.fr/cgi-bin/WebObjects/CandidaDB

Candida genome database: http://www.candidagenome.org/

Finkel, J.S., and Mitchell, A.P. (2010). Genetic control of *Candida albicans* biofilm development. Nat. Rev. Microbiol. *9,* 109–118.

Genolevures: http://www.genolevures.org/yeastgenomes

Liu, Y., and Filler, S.G. (2011). *Candida albicans* Als3, a multifunctional adhesin and invasin. Eukaryot. Cell *10,* 168–173.

Lohse, M.B., and Johnson, A.D. (2009). White-opaque switching in *Candida albicans*. Curr. Opin. Microbiol. *12,* 650–654.

Noble, S.M., and Johnson, A.D. (2007). Genetics of *Candida albicans*, a diploid human fungal pathogen. Ann. Rev. Genet *41,* 193–211.

Sanger Institute: http://www.sanger.ac.uk/Projects/Fungi/

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Primer

Unfolded protein response

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In eukaryotic cells, the endoplasmic reticulum (ER) is a membrane-enclosed interconnected organelle responsible for the synthesis, folding, modification, and quality control of numerous secretory and membrane proteins. The processes of protein folding and maturation are highly assisted and scrutinized but are also sensitive to changes in ER homeostasis, such as Ca^{2+} depletion, oxidative stress, hypoxia, energy deprivation, metabolic stimulation, altered glycosylation, activation of inflammation, as well as increases in protein synthesis or the expression of misfolded proteins or unassembled protein subunits. Only properly folded proteins can traffic to the Golgi apparatus, whereas those that misfold are directed to ER-associated degradation (ERAD) or to autophagy. The accumulation of unfolded/misfolded proteins in the ER activates signaling events to orchestrate adaptive cellular responses. This unfolded protein response (UPR) increases the ER protein-folding capacity, reduces global protein synthesis, and enhances ERAD of misfolded proteins.

In mammals, the UPR is signaled through three ER transmembrane protein sensors (Figure 1): inositol-requiring kinase 1 (IRE1), pancreatic ER eIF2a kinase (PERK), and activating transcription factor 6 (ATF6). The luminal domain of each sensor responds to the level of unfolded/misfolded protein in the ER. If the cell cannot resolve the protein-folding defect, cell-death signaling pathways are activated. As our understanding of ER protein-folding pathways and the mechanisms of UPR signaling of adaptive and apoptotic responses has grown, so has the significance of their impact on the etiology of multiple human pathologies, including metabolic syndrome, neurodegenerative disorders, inflammatory disease and cancer. With this armamentarium of knowledge, it is now possible for rational design of therapeutics to target protein-folding pathways and UPR signaling to resolve protein misfolding in disease states in a manner that was not previously conceivable.

IRE1–XBP1

The most conserved branch of the UPR is mediated by IRE1, a type I transmembrane protein with both a serine/threonine kinase domain and an endoribonuclease (RNase) domain in its cytosolic portion. In yeast, Ire1p is the only identified ER stress sensor. There are two IRE1 homologues in mammals: IRE1α is expressed ubiquitously, whereas IRE1β expression is mostly restricted to the intestinal epithelium.

Two models have been proposed for the activation of IRE1/Ire1p. The first is a competition-binding model that posits unfolded and/or misfolded proteins in the ER lumen compete with Ire1p for binding to the chaperone BiP. Ire1p binding to BiP inhibits signaling, whereas Ire1p released from BiP forms homodimers and oligomers that promote *trans*-autophosphorylation and RNase activation. Alternatively, since the crystal structure of the yeast Ire1p luminal domain revealed the presence of a peptide-binding groove similar to that of major histocompatibility class I molecules, it was proposed that unfolded/misfolded proteins directly bind to the amino-terminal luminal domain of Ire1p to induce dimerization. A recent study showed that unfolded proteins and hydrophobic peptides bind to the core luminal domain of Ire1p, which then undergoes dimerization *in vitro*. In contrast, the peptide-binding cleft in the crystal structure of the luminal domain of human IRE1α is not solvent accessible and the luminal domain does not interact with unfolded proteins *in vitro*. A mutant form of IRE1α that cannot bind to BiP is able to spontaneously dimerize and activate kinase/RNase activities in the absence of ER stress, suggesting that mammalian IRE1α may be released from BiP but may not require peptide binding for activation.

The luminal domain of IRE1α forms homodimers in the plane of the ER membrane, juxtaposing the kinase domains for *trans*-autophosphorylation to stimulate the kinase and RNase activities. These activities initiate the removal of a 26 base intron from the mRNA encoding X-box-binding protein

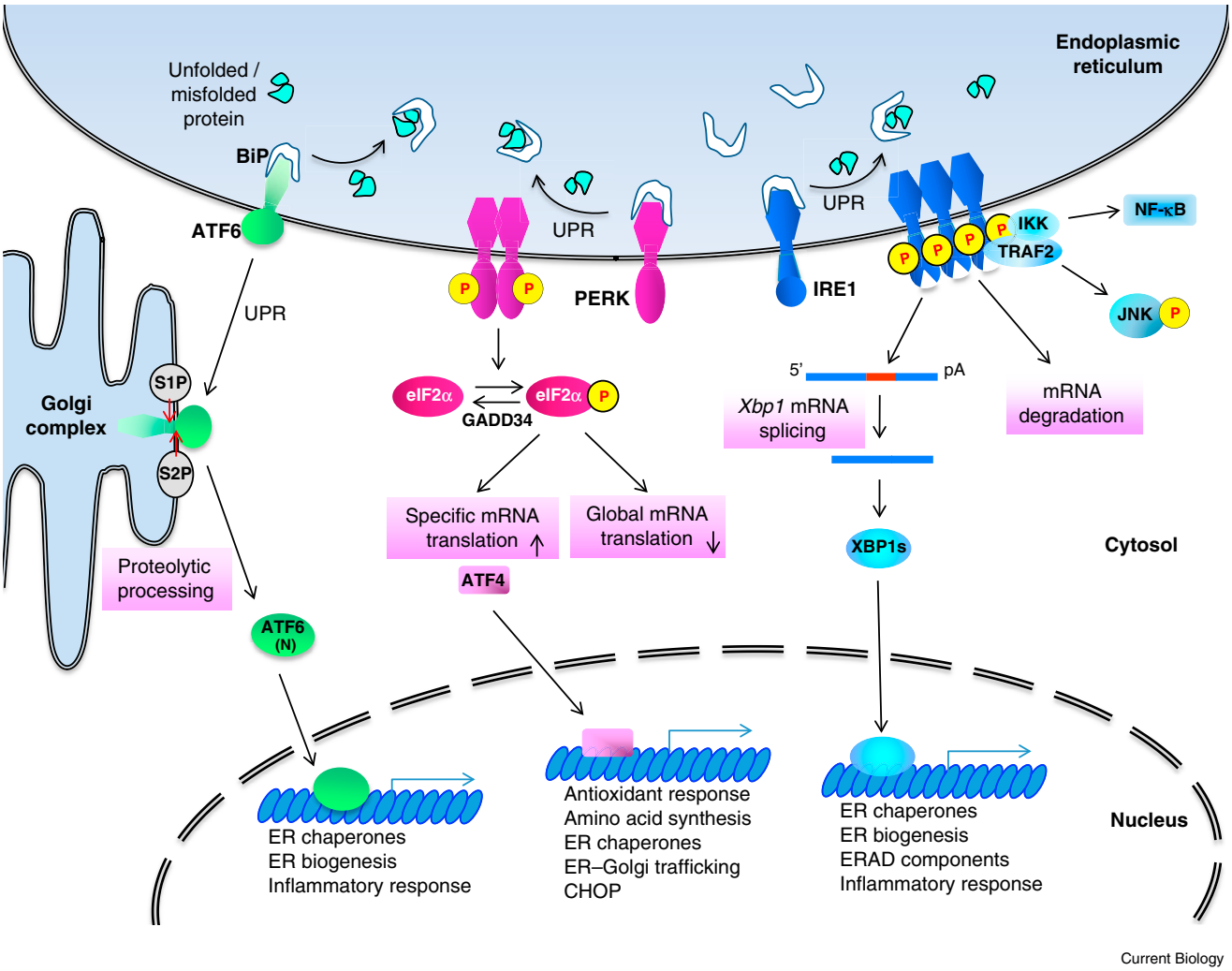

Figure 1. The unfolded protein response in mammals. See main text for details.

1 (XBP1), resulting in a translational frameshift that generates a 41 kDa CREB/ATF basic leucine zipper (bZiP)-containing transcription factor. In addition to selective cleavage of the *Xbp1* mRNA, IRE1 degrades a subset of ER-localized mRNAs in *Drosophila* and in mammalian cells in a stress-dependent manner — termed regulated IRE1-dependent decay of mRNAs (RIDD) — thereby reducing protein synthesis to alleviate ER stress. Analysis of RIDD targets revealed a consensus CUGCAG sequence motif within a stem–loop structure. Recently, a small molecule that specifically binds to and inhibits the activity of the IRE1 RNase domain was shown to abolish *Xbp1* mRNA splicing and RIDD, impeding the expansion of the protein secretory capacity. Previous studies suggested that IRE1β is less active than IRE1α in cleaving *Xbp1* mRNA; instead, it can cleave 28S ribosomal RNA to attenuate mRNA translation and can degrade the mRNA encoding microsomal triglyceride transfer protein to limit chylomicron production and lipid absorption in the small intestine.

As a potent transcription activator, XBP1 binds to the UPR element (UPRE) and to the ER stress-response elements I and II (ERSE-I and ERSE-II) in the promoter regions of target genes. Previous studies suggested that XBP1 induces the expression of a wide range of genes that orchestrate ER protein folding, secretion, quality control and ERAD, and activates phospholipid biosynthesis and ER expansion upon ER stress.

IRE1α–XBP1 signaling plays an important role in a wide spectrum of biological processes, including differentiation, metabolism, inflammation, tumorigenesis and neurodegeneration. Whole-body deletion of *Ire1α* or *Xbp1* in mice is embryonic lethal at 12.5 days of gestation. XBP1 is essential for liver development by inducing the expression of α-fetoprotein and several acute phase response genes that promote hepatocyte differentiation, growth and prevent apoptosis. IRE1α is activated dramatically in murine placenta, while loss of IRE1α reduces vascular endothelial growth factor-A (VEGF-A) expression with severe dysfunction of the labyrinth, which has a highly developed network of blood vessels that are essential for nutrient uptake during fetal development. XBP1 also contributes to expression of the placental carcinoembryonic antigen family of proteins. In addition, IRE1α–XBP1 is required for plasma cell differentiation, development

and survival of dendritic cells, the proinflammatory response in macrophages, the maturation of digestive enzyme-secreting zymogenic cells in the stomach, and the normal function and homeostasis of Paneth cells, a secretory intestinal epithelial cell essential for innate immunity and host defense.

Recently, IRE1α–XBP1 signaling was linked to numerous human diseases, including several cancers, β-cell failure, obesity, rheumatoid arthritis, inflammatory bowel disease, vitiligo, amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Interestingly, the deficiency of XBP1, which functions as a pro-survival transcription factor in multiple disease models, impedes the progression of both ALS and HD by enhancing macroautophagy of mutant SOD1 or huntingtin.

Several pleiotropic transduction pathways have been invoked in XBP1-mediated UPR signaling. Recent studies demonstrated that p38 MAP kinase and the regulatory subunits of phosphoinositide 3-kinase regulate the UPR and insulin sensitivity by increasing the nuclear translocation of XBP1. In *Caenorhabditis elegans*, IRE-1–XBP-1 plays the predominant role in UPR signaling, similar to *Saccharomyces cerevisiae*, with PEK (the *C. elegans* homolog of mammalian PERK) and ATF6 being less important. In *C. elegans*, XBP-1 is essential for larval host protection against ER stress induced by the immune response to bacterial infection. Moreover, in *daf-2* worms that are mutant in insulin/IGF-1 signaling, XBP-1 collaborates with the FOXO transcription factor DAF-16 to enhance ER stress resistance and promote longevity.

As a protein kinase, IRE1α was proposed to integrate UPR signaling with inflammatory responses. Upon ER stress, phosphorylation of IRE1α in the cytosolic domain stimulates its interaction with tumor necrosis factor α (TNFα) receptor-associated factor 2 (TRAF2), an adaptor protein in the TNFα signaling pathway. The IRE1α–TRAF2 complex recruits IκB kinase (IKK), which in turn leads to the phosphorylation and degradation of IκB, resulting in NF-κB activation and upregulation of its downstream inflammatory pathways. The IRE1α–TRAF2 complex also recruits apoptosis signaling kinase (ASK1), which activates c-Jun N-terminal kinase (JNK) to stimulate proinflammatory response signaling via the phosphorylation of the AP1 transcription factor. Additionally, IRE1α–JNK was suggested to activate pro-apoptotic pathways and induce insulin resistance by phosphorylating insulin receptor substrate 1 and 2 in response to ER stress.

PERK–eIF2α–ATF4–CHOP

PERK is a type I transmembrane protein with a cytosolic serine/threonine kinase domain. Although the luminal domains of PERK and IRE1 exhibit limited sequence homology, the predicted structure of the PERK luminal domain is similar to that of the IRE1α luminal domain. Upon ER stress, the chaperone BiP is released from PERK, which then undergoes oligomerization and *trans*-autophophorylation. Indeed, the activation machinery of PERK is quite similar to that of IRE1α. The luminal domain of human PERK can replace the protein misfolding-sensing function of the luminal domain of yeast Ire1p, although yeast does not have a *Perk* gene. Activated PERK phosphorylates Ser51 of the α subunit of eukaryotic translation initiation factor 2 (eIF2α), which in turn attenuates translation initiation to reduce the ER protein-folding load.

In mammals, three additional eIF2α kinases phosphorylate eIF2α at Ser51, each responding to a different stress: the double-stranded RNA-activated protein kinase (PKR) responds to viral infection, ER stress, and nutrient signals; general control non-derepressible-2 (GCN2) is activated during amino-acid starvation; and the heme-regulated inhibitor kinase (HRI) limits protein synthesis in heme-deficient erythroid cells, reduces oxidative stress, and promotes maturation and activation of macrophages. Generally, translation attenuation in response to ER stress is transient due to GADD34-directed dephosphorylation of eIF2α mediated by protein phosphatase PP1. This tight temporal balance of protein synthesis is essential for adaptation because, when protein folding is perturbed, increased transcription of adaptive functions requires mRNA translation to restore protein-folding functions.

The significance of eIF2α phosphorylation in mammals was highlighted by a number of studies. Transgenic mice bearing homozygous knock-in loss-of-function Ser51Ala mutation at the eIF2α phosphorylation site died within 18 hours of birth, due to severe hypoglycemia associated with defective gluconeogenesis in the liver. This was actually the first indication that ER stress is tightly linked with metabolic control. Later it was found that phospho-eIF2α is essential for optimal expression of many UPR genes and is critical for the maintenance of cellular homeostasis and normal function in multiple cell types, including fibroblasts, osteoblasts, hepatocytes, as well as pancreatic endocrine and exocrine cells. A recent study demonstrated that the absence of phospho-eIF2α in pancreatic β cells leads to a severe diabetic phenotype associated with heightened and dysregulated proinsulin translation, proinsulin misfolding, defective ER-to-Golgi transport, diminished expression of β-cell-specific genes, an impaired ER stress response, increased oxidative damage and apoptosis.

In addition to global translational suppression, phospho-eIF2α selectively induces translation of several mRNAs, including that encoding activating transcription factor 4 (ATF4), a 39 kDa bZIP transcription factor that induces transcription of genes encoding ER chaperones, including BiP and GRP94, UPR-associated transcription factors, including XBP1, and intracellular trafficking machinery that is required for ER-to-Golgi trafficking of ATF6 upon ER stress. ATF4 improves cellular homeostasis and function by inducing amino acid biosynthesis and transport, promoting anti-oxidative stress responses, and stimulating the expression of autophagy genes, including *MAP1LC3B*, *ATG12,* and *BECN1*. Recently, ATF4 was shown to orchestrate the proliferation and differentiation of chondrocytes and promote endochondral ossification, by transcriptional activation of the locally secreted factor Indian Hedgehog. In addition, ATF4 drives osteoblast differentiation and controls osteoblast functions, including bone formation, extracellular matrix mineralization, and bioactivity of osteocalcin. Transcription and translation of the cellular inhibitors of apoptosis (XIAP, cIAP1 and cIAP2) are also induced by PERK-mediated phosphorylation of eIF2α in response to ER stress.

One of the downstream targets of eIF2α–ATF4 is CCAAT/enhancer-binding protein homologous protein (CHOP), a 29 kDa bZIP transcription factor whose promoter contains

the binding sites for several major transactivators of the UPR, including ATF4 and ATF6. CHOP is an important mediator of ER stress-induced apoptosis. CHOP activates a number of pro-apoptotic factors, including death receptor 5 (DR5), Bim (a pro-apoptotic member of BCL-2 family), and telomere repeat binding factor 3 (TRB3), and inhibits the anti-apoptotic protein BCL-2. Moreover, CHOP causes oxidative stress by inducing ERO1α, which transfers electrons from protein disulfide isomerase to O_2 to produce H_2O_2. ERO1α also promotes Ca^{2+} release from the ER through the inositol 1,4,5-trisphosphate receptor. Since Ca^{2+} is required for ER chaperone function and for protein folding, depletion of ER Ca^{2+} further disrupts protein folding. Ca^{2+} released from the ER is loaded into mitochondria leading to oxidative stress and pro-apoptotic signaling. In addition, CHOP induces transcription of *Gadd34*, which encodes a regulatory subunit of PP1 that dephosphorylates eIF2α, thereby increasing protein synthesis. If CHOP is induced when protein folding is compromised, the increase in protein synthesis would accentuate oxidative stress and pro-apoptotic signaling. Consistent with these observations, deletion of *Chop* is protective against ER-stress-induced apoptosis in multiple cell types, including fibroblasts, pancreatic β cells, macrophages, and smooth muscle cells, and CHOP should therefore be considered a promising target for treating diseases such as cancer, type 2 diabetes, atherosclerosis, and diseases associated with protein misfolding.

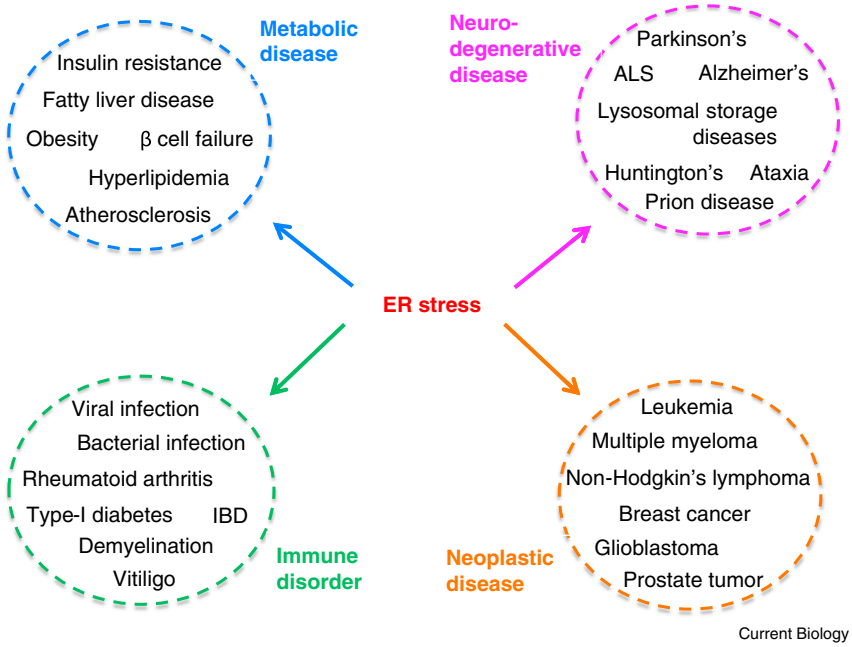

Figure 2. Endoplasmic reticulum stress in human disease.
A number of human diseases are associated with ER protein-folding defects and the UPR. Studies of ER stress and the UPR should enhance our understanding of the pathogenesis of these diseases and open up new avenues to therapeutic approaches.

ATF6

ATF6 is a type II ER transmembrane protein with a CREB/ATF bZIP transcription factor domain at the amino terminus. Upon accumulation of unfolded protein in the ER, ATF6 is released from BiP for trafficking to the Golgi apparatus where it is sequentially cleaved by site 1 and site 2 proteases at the transmembrane site, yielding a cytosolic fragment known as ATF6 p50, which migrates to the nucleus to activate gene expression. The process by which ER-localized bZIP transcription factors translocate from the ER to the Golgi for cleavage to produce functional forms is termed regulated intramembrane proteolysis (RIP).

Mammals have two ATF6 homologues, ATF6α and ATF6β. In mammalian cells, ATF6α can function as a homodimer and bind to ERSE motifs in promoter regions to transactivate ER chaperone genes, such as *Bip* and *p58^{IPK}*. Moreover, ATF6α can heterodimerize with XBP1 in response to ER stress and induce the expression of ERAD components, such as EDEM, HERP and HRD1. Unlike mice lacking XBP1 and ATF4, *Atf6*α-null mice do not exhibit apparent abnormalities under normal conditions. However, ATF6α is essential for optimal protein folding, secretion, and degradation in response to ER stress. As a consequence, ATF6α-deficient cells cannot recover from acute ER stress. Additionally, ATF6α was proposed to induce ER quality control genes by recruiting the CREB-regulated transcription coactivator 2 (CRTC2) to ER stress-inducible promoters, and to downregulate hepatic gluconeogenesis by disrupting the CREB–CRTC2 interaction, thereby diminishing CRTC2 binding to the promoters of gluconeogenic genes in hepatocytes. In contrast, *Atf6*β-null mice do not have a significant phenotype, even when challenged with ER stress. To date, genes regulated by *Atf6*b have not been identified.

Surprisingly, *Atf6*α and *Atf6*β double knockout mice die at a very early embryonic stage, suggesting that an overlapping function of the two isoforms is essential during early embryonic development.

In addition to ATF6, additional RIP-regulated bZIP transcription factors have been identified, including Luman/CREB3, OASIS/CREB3L1, and CREBH/CREB3L3. ER stress induces both transcription and proteolytic processing of Luman, resulting in its binding to ERSE-II and induction of expression of the ERAD protein HERP. OASIS is proteolytically activated during ER stress. Similar to ATF4, OASIS plays an important role in bone formation. OASIS is highly expressed in osteoblasts, where it transactivates the gene encoding type I collagen through a UPRE-like sequence in the promoter region. Moreover, OASIS transcription is induced upon ER stress in astrocytes of the brain, where it activates expression of BiP and prevents ER stress-induced cell death. Recent studies demonstrated that OASIS is required for the terminal differentiation of colonic goblet cells and mucin secretion from these cells. CREBH, a hepatocyte-specific transcription factor, is induced by proinflammatory cytokines, including interleukin-6 and

TNFα, and is proteolytically activated upon ER stress. In contrast to ATF6α, CREBH does not induce UPR gene expression; instead, it induces the expression of genes encoding components of the systemic arm of the innate immune response — the acute phase response — including C-reactive protein and serum amyloid P component. Recent studies demonstrated that CREBH-mediated transcription is required for optimal gluconeogenesis and lipid metabolism in the liver. Importantly, mutant *Crebh* alleles that result in non-functional CREBH or reduced levels of CREBH were identified in patients with extreme hypertriglyceridemia, indicating the physiological significance of CREBH in lipid homeostasis.

ER stress and the UPR in therapeutics

Since ER stress may contribute to the pathogenesis of multiple human diseases (Figure 2), this signaling nexus may be exploited as a therapeutic target for pharmacological intervention. Tauroursodeoxycholate (TUDCA) and 4-phenylbutyrate (PBA) alleviate ER stress by acting as chemical chaperones to prevent protein misfolding and aggregation in the cell. TUDCA and PBA are agents approved by the Food and Drug Administration (FDA) for the treatment of primary biliary cirrhosis and urea-cycle disorders, respectively. Both compounds promote the folding and intracellular trafficking of the mutant Z allele of α1-antitrypsin and the Δ508 cystic fibrosis transmembrane regulator, and ameliorate type 2 diabetes by reducing chronic ER stress and insulin resistance in the tissues of animals and humans with metabolic syndrome. In addition, TUDCA and PBA are in clinical trials for the treatment of many diseases that are associated with protein-folding defects and ER stress, including cystic fibrosis, ALS, HD, and spinal muscular atrophy. Given the excellent safety profiles of both compounds in humans, these agents may be developed as novel therapies for these diseases by restoring cellular protein-folding homeostasis.

Guanabenz is an FDA-approved drug for hypertension that selectively inhibits GADD34-mediated dephosphorylation of eIF2α and exerts a cytoprotective effect against ER stress by prolonging eIF2α phosphorylation and translation attenuation. As eIF2α phosphorylation is protective in many pathologic conditions such as β-cell failure, diabetes, Alzheimer's disease, prion disease, and immune-mediated demyelination in the central nervous system, guanabenz may be a promising candidate for the treatment of these diseases. ER luminal Ca^{2+} is critical for proper protein folding and maturation, and Ca^{2+} leakage from the ER is sufficient to induce ER stress, mitochondrial damage and oxidative stress in the cell. Diltiazem and verapamil are FDA-approved hypertension drugs that stabilize ER Ca^{2+} levels and improve ER protein folding. Future studies should test the therapeutic potential of these compounds in ER stress-associated disease models.

Multiple myeloma cells rely on the IRE1α–XBP1-mediated UPR to cope with the high burden of immunoglobulin folding and secretion. Human studies suggest that spliced *Xbp1* mRNA (*XBP1s*) is an independent prognostic marker for multiple myeloma where patients with low *XBP1s* have a significantly higher survival rate. A small molecule that inhibits IRE1α RNase to prevent *Xbp1* mRNA splicing enhanced apoptosis of multiple myeloma cells induced by proteosome inhibitors. This synergistic effect was associated with increased pro-apoptotic UPR signaling. Future studies should examine whether inhibition of *Xbp1* splicing exhibits selective cytotoxicity toward other cancer cells with high protein secretory activity, such as mammary cancer cells and insulinoma cells. Given the critical role of IRE1α–XBP1 signaling in multiple normal cell types *in vivo*, it is important to examine whether the long-term use of IRE1α inhibitors will negatively affect the function of certain tissues/organs, including the pancreas, liver, and immune system.

In addition to pharmacological manipulations, forced expression of pro-survival UPR genes in specific tissues by gene therapy has shown promise for several neurodegenerative diseases. The local delivery of the *Bip* gene mitigated neuronal degeneration and disease symptoms of autosomal dominant retinitis pigmentosa and Parkinson's disease in rodent models. The overexpression of the ER chaperone GRP94 alleviated spinal cord injury in a rat model.

Perspectives

Our recent insights indicate that protein-folding homeostasis in the ER plays critical roles in eukaryotic cell function and that the UPR is an essential regulatory hub that interacts with all aspects of cell signaling at the transcriptional, translational and post-translational levels. Despite all this progress, there is still a need to understand what factors limit ER protein-folding efficiency for specific proteins in different cell types. Our understanding of the impact of protein misfolding in the ER and the UPR has also extended to a broad spectrum of normal organismal physiological functions and pathological conditions. Future studies should further our understanding of how the UPR interacts with other signal transduction pathways in different cell types and the tissue-specific roles of the ER stress sensors, transducers, and effectors under various pathophysiological conditions. Protein misfolding in the ER and the UPR are promising therapeutic targets for multiple human diseases. We can now test the therapeutic potential of these targets by generating tissue-specific deletion/overexpression animal models and by identifying small molecules that specifically target selective UPR components.

Further reading

Back, S.H., and Kaufman, R.J. (2012). Endoplasmic reticulum stress and type 2 diabetes. Annu. Rev. Biochem. *81*, 767–793.

Hotamisligil, G.S. (2010). Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell *140*, 900–917.

Kohno, K. (2007). How transmembrane proteins sense endoplasmic reticulum stress. Antioxid. Redox Signal. *9*, 2295–2303.

Martinon, F., and Glimcher, L.H. (2011). Regulation of innate immunity by signaling pathways emerging from the endoplasmic reticulum. Curr. Opin. Immunol. *23*, 35–40.

Matus, S., Glimcher, L.H., and Hetz, C. (2011). Protein folding stress in neurodegenerative diseases: a glimpse into the ER. Curr. Opin. Cell Biol. *23*, 239–252.

Smith, M.H., Ploegh, H.L., and Weissman J.S. (2011). Road to ruin: targeting proteins for degradation in the endoplasmic reticulum. Science *334*, 1086–1090.

Tabas, I., and Ron, D. (2011). Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. Nat. Cell Biol. *13*, 184–190.

Walter, P., and Ron, D. (2011). The unfolded protein response: from stress pathway to homeostatic regulation. Science *334*, 1081–1106.

Wang, S., and Kaufman, R.J. (2012). The impact of the unfolded protein response on human disease. J. Cell Biol. *197*, 854–855.

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